REMARKS

Claims 1-24 are currently pending in this application. Claims 7-12 and 19-24 have been withdrawn from consideration. By this amendment, claims 1, 2, 4, 13, 14 and 16 have been amended. No new matter has been entered by these amendments. Examiner Li's comments in the April 27, 2005 Office Action have been carefully considered and reconsideration of this application in view of the current amendments and following remarks is respectfully requested.

Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 1-5 and 13-17 have been rejected as not enabled by the specification under 35 U.S.C. § 112, first paragraph. Specifically, the Examiner stated that while the specification is enabling for a method for treating atrial tachyarrhythmia or inhibiting the onset of atrial tachyarrhythmia in a subject by administering to the subject an effective amount of the agent disclosed in the specification, the specification "does not reasonably provide enablement for such a method of employing a genus of agents that inhibits PKA phosphorylation of RyR2 receptor or dissociation of FKBP12.6 from RyR2 receptor." (4/27/05 Office Action, p. 3). According to the Examiner the claims of applicants' invention:

> are drawn to a method comprising administration of a genus of structurally undefined agents. However, the specification merely discloses an agent, JTV-519, and other compounds derived from 1,4-benzothiazepine (page 28, lines 31-34). The specification fails to provide the characteristic structure that is critical for the function of the claimed genus of agents and fails to provide sufficient guidance and/or working examples on how to make such a genus of agents. ... Therefore, it would require undue experimentation for one skilled in the art to make the genus of agents and to use the agents in the claimed methods commensurate in scope with the claims.

(4/27/05 Office Action, pp. 4-5).

The examiner also rejected claims 1-5 and 13-17 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time

the application was filed, had possession of the claimed invention. Specifically, the examiner stated:

> The specification fails to provide any critical structural feature to adequately describe the genus of agents that may be administered in the claimed methods. The specification merely discloses an agent, JTV-519, and other compounds derived from 1,4-benzothiazepine (page 28, lines 31-34), which are not sufficiently representative of the claimed genus of agents. There is no defined relation between function and structure of the agents in the specification. There is even no identification of any particular portion of the structure that must be conserved. ... Furthermore, although teaching a number of agents that inhibits (sic) PKA phosphorylation of RyR2 receptor or dissociation of FKBP12.6 from RyR2 receptor ...the prior art does not provide compensatory structural or correlative teachings to enable one skilled in the art to identify the encompassed compounds as being identical to those instantly claimed.

(4/27/05 Office Action, pp. 6-7).

Applicants respectfully traverse this rejection and submit that the description of the present application sufficiently enables a skilled artisan to practice the claimed invention without undue experimentation. Applicants further submit that the specification and claims adequately convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time the application was filed. However, in order to expedite the prosecution of this application, but without conceding the correctness of the examiner's position, applicants have amended claims 1 and 13 to more particularly point out that the claimed agent is a derivative of 1,4-benzothiazepine. Support for these amendments may be found throughout the instant specification and specifically at page 74, lines 20-23. Accordingly, no new matter has been added by these amendments.

The claimed invention provides methods for treating and preventing atrial tachyarrhythmias in a subject by administering to the subject an agent which inhibits PKA phosphorylation of a type 2 ryanodine receptor. These methods are specifically described throughout the specification such that one of ordinary skill in the art could practice the

claimed methods without undue experimentation, and such that it would be clear to one of ordinary skill in the art that the inventors had possession of the claimed invention at the time the application was filed. (See e.g., the subject specification at page 28, lines 3-7; page 29, lines 21-33; page 73, line 31 – page 77, line 13).

The specification specifically describes in detail assays for monitoring the effects of test agents on RyR2 ion channel function (Instant Specification, page 73, line 31 – page 77, line 13). The specification specifically states: "An example of an agent that inhibits the dissociation of FKBP12.6 from RyR2 is JTV-519 (also known as K20) or any other compound in this class of compounds that are derivatives of 1,4-benzothiazepine)" (Instant Specification, page 74, lines 20-23). Additionally, the specification provides working examples demonstrating anti-arrhythmic effects utilizing JTV-519 and applicable to any 1,4-benzothiazepine derivative (Instant Specification, page 92 line 26 – page 93, line 20).

Applicants respectfully point out that the scope of enablement is that which is disclosed in the specification plus the scope of that which would be known to one of ordinary skill in the art without undue experimentation. In view of the assays and working examples provided by the specification, one of ordinary skill in the art following the description of the specification would be able to practice the claimed methods without undue experimentation. Specifically, the skilled artisan could identify 1,4-benzothazepine derivatives which demonstrate efficacy in the claimed methods by following the assays described throughout the specification, and specifically at page 73, line 31 – page 77, line 13. The working examples provided throughout the specification, and specifically at page 92 line 26 – page 93, line 20, would enable a skilled artisan to treat subjects afflicted with atrial tachyarrhythmias and prevent atrial tachyarrhythmias in a subject by administering to the subject an agent which inhibits PKA phosphorylation of RyR2 in the subject's heart, without undue experimentation. These assay descriptions and working examples would also clearly indicate to the skilled artisan that the inventors had possession of the claimed invention at the time the application was filed.

Accordingly, in view of the amendments to claims 1 and 13 and the above remarks, applicants respectfully request withdrawal of the examiner's 35 U.S.C. § 112, first paragraph, rejection of claims 1-5 and 13-17.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 2, 4-6, 14 and 16-18 were rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Specifically, the examiner stated that the claims are indefinite because they recite "FKBP12.6 binding protein" and that neither the specification nor the art defines "a FKBP12.6 binding protein."

In response, applicants respectfully point out that the subject disclosure refers repeatedly to "FKBP12.6" as a "binding protein" which binds to and regulates the RyR2 receptor channel. See e.g., the specification at page 24, lines 11-15: "'FKBP12.6' means a FK-506 binding protein, having a molecular weight of about 12,000 daltons, that binds to and regulates the gating (activation and inactivation) of the RyR2 receptor channel." The term is described further at page 2, lines 9-17 of the specification:

> The RyR2 receptor is a tetramer comprised of four 565,000 dalton RyR2 polypeptides and four 12,000 dalton FK-506 binding proteins (FKBPI2.6). FKBP12s are regulatory subunits that stabilize RyR2 channel function (Brillantes, *et at., 1994)* and facilitate coupled gating between neighboring RyR2 channels (Marx, *et at.,* 1998). The latter are packed into dense arrays in specialized regions of the sarcoplasmic reticulum that release intracellular stores of Ca +2, triggering muscle contraction.

The specification of the parent patent, *i.e.,* U.S. Patent No. 6,489,125, which was incorporated by reference into the present application, further states: "One FKBP12 molecule is bound to each RyR2 subunit." Because the term "FKBP12.6 binding protein" is described throughout both the literature and the parent patent, this term is a term of art, the definitive meaning of which would be clear to one of skill in the art.

Notwithstanding applicants above remarks, in order to expedite the prosecution of this application, but without conceding the correctness of the examiner's position, applicants have amended claims 2, 4-6, 14 and 16-18 to replace the claim term "FKBP12.6 binding protein" with the term "FKBP12.6". Support for these amendments is found throughout the subject specification, and specifically at page 24, lines 11-15. Accordingly, these amendments do not include new matter. In view of these amendments, applicants respectfully request withdrawal of the examiner's 35 U.S.C. § 112, second paragraph, rejection of claims 2, 4-6, 14, and 16-18.

Rejections Under 35 U.S.C. § 102(b)

Claims 1-6 and 13-18 were rejected under 35 U.S.C. § 102(b) as anticipated by Nakaya *et al.*, *British Journal of Pharmacology*, 131:1363-1372 (2000) as evidenced by Yano *et al.*, *Circulation*, 107:477-484 (2003). Specifically, the examiner stated:

> Nakaya *et al.* teach inhibitory effects of JTV-519 on experimental atrial fibrillation in Langendorff-perfused guinea-pig hearts. Nakaya *et al.* teach that perfusion of carbachol (1μM) shortened monophasic action potential and effective refractory period, and lowered atrial fibrillation threshold of the guinea-pig hearts. Addition of JTV-519 (1μM) inhibited the induction of atrial fibrillation by prolonging monophasic action potential and effective refractory period ... Nakaya *et al.* further [teach] (sic) that JTV-519 exerts antiarrhythmic effects against atrial fibrillation... JTV-519 is known in the art to inhibit PKA phosphorylation of RyR2 receptor and dissociation of FKBP12.6 from the RyR2 receptor, as evidenced by Yano *et al.*... Thus, the reference of Nakaya *et al.* meets the limitations of claims 1-6 and 13-18.

(4/27/05 Office Action, pp. 8-9).

Applicants respectfully traverse this rejection. The Nakaya *et al.* reference does not qualify as prior art under 35 U.S.C. § 102(b) because it was not published more than one year prior to the effective filing date of the instant application. In fact, Nakaya *et al.* was published December 2000, at least six month after the May 10, 2000 effective filing date of this application. Accordingly, applicants respectfully request withdrawal of this rejection.

Further, Nakaya *et al.* as evidenced by Yano *et al.* do not teach or otherwise suggest every element of applicants' claimed invention. Nakaya *et al.* teach that JTV-519 shows antiarrhythmic efficacy against atrial fibrillation in isolated guinea pig hearts by inhibiting muscarinic acetylcholine receptor-operated K^+ currents. Nakaya *et al.* does not teach applicants invention, i.e., a method for treating a subject afflicted with atrial tachyarrhythmia by administering to the subject an agent which inhibits PKA phosphorylation of RyR2 in the subject's heart. Additionally, Nakaya *et al.* does not teach any method for inhibiting the onset of atrial tachyarrhythmias in a subject by administering to the subject an agent which inhibits PKA phosphorylation of RyR2 in the subject's heart.

Nakaya *et al.* is specifically directed to the effect of JTV-519 on muscarinic acetylcholine receptor-operated K+ current in isolated guinea-pig atrial cells. In contrast, applicants' invention is directed to the nicotinic acetylcholine receptor, specifically cAMP dependent protein kinase (PKA) and tyrosine specific protein kinase. The two types of acetylcholine receptors, nicotinic and muscarinic, constitute different molecular entities. Not only is Nakaya *et al.* directed to different acetylcholine receptors but Nakaya *et al.* is directed to a different electrophysiological effector, *i.e.,* the potassium ion. Unlike Nakaya *et al.*, the electrophysiological effector of the present invention is the calcium ion. Nakaya *et al.* does not discuss ryanodine receptors.

Moreover, contrary to the examiner's assertions, Yano *et al.* does not remedy the deficiencies of Nakaya *et al.* as discussed above. Yano *et al.* teach that JTV-519 reverses the decrease in the stoichiometric ratio for FKBP12.6 binding to ryanodine receptor in the sarcoplasmic reticulum in dog models of heart failure. Yano *et al.* does not teach or otherwise suggest methods for treating and preventing atrial tachyarrhythmias. Therefore, applicants invention is patentably distinct from Nakaya *et al.* as evidenced by Yano *et al.* because neither publication teaches methods for treating or preventing atrial tachyarrhythmias by administering an agent which inhibits PKA phosphorylation of RyR2 receptors. Accordingly, in view of the forgoing remarks, applicants respectfully request that the examiner withdraw the 35 U.S.C. § 102(b) rejection of claims 1-6 and 13-18.

CONCLUSION

In view of the foregoing amendments and remarks, applicants believes that they have fully responded to the Examiner's concerns and that each of the pending claims is in condition for immediate allowance. Accordingly, applicants respectfully request consideration and immediate allowance of all the pending claims.

Applicants request that any questions concerning this matter be directed to the undersigned at (973) 660-4414.

The Commissioner is hereby authorized to charge $60 for the one month extension of time to Deposit Account No. 50-1698. Authorization is also given to charge any additional fees that may be required or credit any overpayment to Deposit Account No. 50-1698.

Respectfully submitted,

August 29, 2005
Date

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